Facile Substitution of *N*,*N*-Dimethylanilines and Phenols with Trifluoroacetaldehyde Ethyl Hemiacetal

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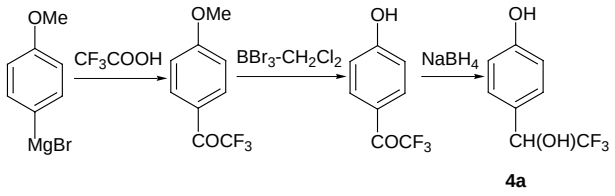
Abstract: 2,2,2-Trifluoro-1-(*N*,*N*-dimethylaminophenyl)ethanols were easily formed in excellent yields by electrophilic substitution between *N*,*N*-dimethylanilines **1a, b** and trifluoroacetaldehyde ethyl hemiacetal (TFAE). The corresponding substitution of phenols **2a-e** to prepare 2,2,2-trifluoro-1-(hydroxyphenyl)ethanols, however, occurred only in the presence of catalytic amounts of anhydrous potassium carbonate.

Key words: α-trifluoromethylbenzylic alcohol, *N*,*N*-dimethylaniline, phenol, trifluoroacetaldehyde ethyl hemiacetal, aromatic substitution

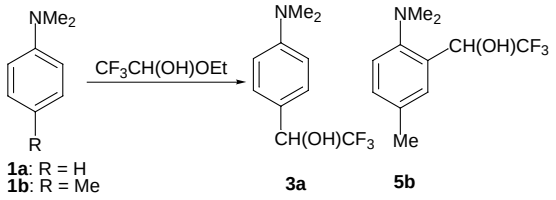
Trifluoromethylated compounds have attracted much attention because of their unique properties,[1] and the development of new preparation methods is still an important area of research.[2] α-Trifluoromethylbenzylic alcohols, especially the optically active ones, are of great interest because of their potential use as ferroelectric liquid crystals.[3] For practical applications, *p*-substitutents such as hydroxyl or amino groups, are introduced into their benzene rings.[4] Compound **4a** is one of the most important intermediates used for this. It is usually prepared by Grignard reaction of *p*-anisylmagnesium bromide and trifluoroacetic acid, followed by demethylation and reduction (Scheme 1).[5]



Scheme 1

Trifluoroacetaldehyde, a potentially very useful precursor to trifluoromethyl carbinols, is rarely used directly because of the volatility and the commercial unavailability. For this reason trifluoroacetaldehyde ethyl hemiacetal (TFAE) is usually used as an important synthetic equivalent.[6] Its substitution reaction with electron-rich heteroarenes, such as indoles and imidazoles, readily occurs under mild conditions.[7] In our continuing investigations, substitutions of TFAE with electron-rich benzene derivatives have been carried out to prepare useful α-trifluoromethylbenzylic alcohols. We here report its reactions with *N*,*N*-dimethylanilines and with phenols.

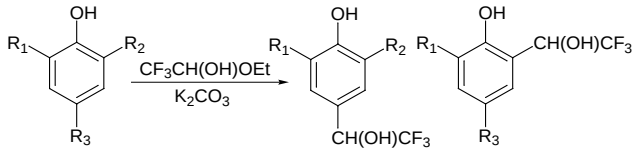
The reaction was carried out by heating equivalent amounts of *N*,*N*-dimethylanilines **1a, b** and TFAE at 120 °C[8] (Scheme 2). 2,2,2-Trifluoro-1-[4-(dimethylamino)phenyl]ethanol **3a**[9] was the main product in the reaction of *N*,*N*-dimethylaniline **1a**, only a trace amount of the *o*-substituted isomer being detected by GC. When the para site was blocked by a methyl group, i.e. **1b**, the *o*-substituted product 2,2,2-Trifluoro-1-[2-(dimethylamino)-5-methylphenyl] ethanol **5b** was the only product.



Scheme 2

On the other hand, no reaction occurred between **2a-e** and TFAE under the same conditions. In the presence of catalytic amounts of anhydrous potassium carbonate, however, these reactions proceeded smoothly and gave rise to the formation of the substituted products, [10] 2,2,2-trifluoro-1-(hydroxyphenyl)ethanols (Scheme 3). Details of these reactions are given in Table 1. Both the *p*- and *o*-substituted products,[11] **4a** and **6a,** were formed in the reaction of phenol **2a**, the ratio of **4a**/**6a** being higher at a lower temperature. When the reaction was performed at 120 °C, a certain amount of di-substituted product **4a'** was also formed. In the case of 2,6-dimethylphenol **2c**, however, only the *p*-substituted product **4c**[12] was generated even if the reaction occurred at 120 °C. Moreover, only the *o*-substituted products were formed in the reactions of 4-methylphenol **2b** and 4-phenylphenol **2e**, though mono-substituted product **6b** was the predominant product for **2b**, but both mono- and di-substituted products **6e** and **6e'** were formed for **2e**.

In conclusion, the substitution of *N*,*N*-dimethylanilines or phenols with trifluoroacetaldehyde ethyl hemiacetal is an appropriate pathway to prepare α-trifluoromethylbenzylic alcohols. Further applications of this substitution are being investigated.



2a: R_1=R_2=R_3=H;
2b: R_1=R_2=H, R_3=Me;
2c: R_1=R_2=Me, R_3=H;
2d: R_1=MeO,R_2=R_3=H;
2e: R_1=R_2=H, R_3=Ph

4a: R_1=R_2=H;
4a': R_1=H, R_2=CH(OH)CF_3
4c: R_1=R_2=Me;
4d: R_1=MeO, R_2=H
4d': R_1=MeO, R_2=CH(OH)CF_3

6a: R_1=R_3=H;
6b: R_1=H, R_3=Me;
6d: R_1=MeO, R_3=H
6e: R_1=H, R_3=Ph
6e': R_1=CH(OH)CF_3 R_3=Ph

Scheme 3

Table 1 Substitution of *N,N*-dimethylanilines and phenols using trifluoroacetaldehyde ethyl hemiacetal.[a]

Substrates	Conditions	yields (%)[b]	
1a	120 °C, 6 h	**3a** (92)	
1b	120 °C, 30 h	**5b** (58)	
2a	120 °C, 6 h	**4a** (48)	**6a** (20)
		4a' (7)	
2a	60 °C, 12 h	**4a** (65)	**6a** (10)
2b	120 °C, 6 h	**6b** (91)	
2c	120 °C, 6 h	**4c** (92)	
2d	120 °C, 6 h	**4d** (33)	**6d** (11)
		4d' (12)	
2d	60 °C, 72 h	**4d** (48)	**6d** (3)
		4d' (6)	
2e	120 °C, 30 h	**6e** (43)	**6e'** (22)

[a] All experiments were done on the 30 mmol scale, and 5 mol% of K_2CO_3 was used for **2a-2e**. [b] Isolated yields based on the substrates.

References and Notes

(1) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, Elsevier, Amsterdam, 1993. Resnati, G. *Tetrahedron* **1993**, *49*, 9385. Kitazume, T.; Lin, J. T.; Yamazaki, T. *Tetrahedron: Asymmetry* **1991**, *2*, 235. Banks, R. E. Ed. *Preparation, Properties and Industrial Applications of Organofluorine Compounds*, Ellis Horwood, Chichest, 1982.

(2) Xu, Y.; Dolbier, Jr. W. R. *Tetrahedron Lett*. **1998**, *39*, 9151. Prakash, G. K.; Yudin, K. A. *Chem. Rev*. **1997**, *97*, 757. Loh, T. P.; Li, X. R. *Tetrahedron Lett*. **1997**, *38*, 869. Bravo, P.; Resnati, G. *Tetrahedron: Asymmetry* **1990**, *1*, 661. McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555. Konno, T.; Nakao, H.; Kitazume, T. *J. Fluorine Chem*. **1997**, *86*, 81. Singh, R. P.; Cao, G.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem*. **1999**, *64*, 2579.

(3) Nohira, H. *J. Synth. Org. Chem. Jpn*. **1991**, *49*, 467. Walba, D. M.; Razavi, H. A.; Clark, N. A.; Parnar, D. S. *J. Am. Chem. Soc*. **1988**, *110*, 8686.

(4) Fujisawa, T.; Sugimoto, T.; Shimizu, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1095.

(5) Creary, X. *J. Org. Chem*. **1987**, *52*, 5027. Fujisawa, T.; Ichikawa, K.; Shimizu, M. *Tetrahedron: Asymmetry* **1993**, *4*, 1237. Fujisawa, T.; Onogawa, Y.; Sato, A.; Mitsuya, T.; Shimizu, M. *Tetrahedron* **1998**, *54*, 4267.

(6) Loh, T. P.; Li, X. R. *J. Chem. Soc., Chem. Commun*. **1996**, 1929. Kubota, T.; Iijima, M.; Tanaka, T. *Tetrahedron Lett*. **1992**, *33*, 1351. Sakumo, K.; Kuki, N.; Kuno, T.; Takagi, T.; Koyama, M.; Ando, A.; Kumadaki, I. *J. Fluorine Chem*. **1999**, *93*, 165. Olah, G. A.; Wang, Q.; Li, X.-Y.; Parakash, G. K. S. *Synlett* **1993**, *1*, 32. Mikami, K.; Takasaki, T.; Matsukawa, S.; Maruta, M. *Synlett* **1995**, *10*, 1057.

(7) Fujii, S.; Maki, Y.; Kimoto, H. *J. Fluorine Chem*. **1986**, *30*, 415. Maki, Y.; Kimoto, H.; Fujii, S.; Senga, M.; Cohen, L. A. *J. Fluorine Chem*. **1988**, *39*, 47.

(8) Typical procedure: A mixture of 3.63 g (30 mmol) of *N,N*-dimethylaniline and 4.32 g (30 mmol) of trifluoroacetaldehyde ethyl hemiacetal was heated with stirring at 120 °C for 6 h. After being cooled, the mixture became a solid cake. The crude product was then recrystallized in CH_2Cl_2 to give the pure compound **3a**.

(9) **3a**: white solid; m.p. 98-99 °C; ^{1}H NMR ($CDCl_3$, TMS) δ 2.55 (1 H, br, s), 2.94 (6 H, s), 4.85 (1 H, q, *J* = 6.5 Hz), 6.70 (2 H, d, *J* = 8.7 Hz), 7.29 (2 H, d, *J* = 8.7 Hz). ^{19}F NMR ($CDCl_3$, C_6F_6), δ 85.81 (d, *J* = 6.5 Hz). MS *m/z* 219 (M^+, 94), 150 (100). Anal. calcd. for $C_{10}H_{12}NOF_3$ C% 54.77; H% 5.52, N% 6.39. Found C% 54.56, H% 5.46, N% 6.55.

(10) Typical procedure: A mixture of 2.82 g (30 mmol) of phenol, 4.32 g (30 mmol) of trifluoroacetaldehyde ethyl hemiacetal and 0.21 g (1.5 mmol) of anhyd K_2CO_3 was heated with stirring at 60 °C for 12 h. After being cooled, the mixture was dissolved in Et_2O, washed with water, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (9:1 to 5:1 hexane: EtOAc), **6a** (0.58g, 10%) and **4a** (3.74g, 65%) being collected.

(11) **4a**: white solid; mp 123.5-125 °C. ^{1}H NMR (acetone-d_6, TMS) δ 5.30 (2 H, br, s), 5.06 (1 H, q, *J* = 7.4 Hz), 6.86 (2 H, d, *J* = 8.5 Hz), 7.36 (2 H, d, *J* = 8.5 Hz). ^{19}F NMR (acetone-d_6, C_6F_6), δ 85.73 (d, *J* = 7.4 Hz). MS *m/z* 192 (M^+, 38), 123 (100). HRMS. Calculated: 192.0398. Found: 192.0398. **6a**: white needle; m.p. 118 – 118.5 °C. ^{1}H NMR (acetone-d_6, TMS) δ 2.87 (2 H, br, s), 5.57 (1 H, q, *J* = 7.4 Hz), 6.91 (2 H, m), 7.17 (1 H, dd, *J* = 7.0 Hz and 2.0 Hz), 7.50 (1 H, d, *J* = 7.0 Hz). ^{19}F NMR (acetone-d_6, C_6F_6), δ 85.94 (d, *J* = 7.4 Hz). MS *m/z* 192 (M^+, 55), 174 (18), 146 (40), 123 (95), 77 (100). HRMS. Calculated: 192.0398. Found: 192.0378.

(12) **4c:** white solid; mp 136-138 °C. ^{1}H NMR ($CDCl_3$, TMS) δ 2.25 (6 H, s), 4.88 (1 H, q, *J* = 7.2 Hz), 5.12 (2 H, br, s), 7.07 (2 H, s). ^{19}F NMR ($CDCl_3$, C_6F_6), δ 85.91 (d, *J* = 7.2 Hz). MS *m/z* 220 (M^+, 60), 151 (100). HRMS. Calculated: 220.0711. Found: 220.0711.

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